Liver is the hub of metabolic activity of the body. Indeed, most drugs are modified or metabolized in the liver. Thus, drugs that are dependent primarily on the liver for their systemic clearance are likely to have reduced elimination and subsequent accumulation, leading to excessive plasma drug concentrations and adverse effects. However, the effects of hepatic insufficiency on the pharmacokinetics of drugs are not consistent or predictable. Furthermore, the influence of hepatic disease on different drugs can be variable, despite their sharing the same metabolic pathway. Problems in forecasting drug kinetic behaviour are further enhanced by the additional impairment of kidney function which often ensues in advanced liver diseases.

**PATHOPHYSIOLOGY**

Liver disease can enhance the risk of adverse reactions by several mechanisms and therefore drug prescribing should be carefully done in all patients with severe liver disease. The main problems occur in patients with cirrhosis, especially those with jaundice, ascites or encephalopathy. Some of the reasons are given below.

**Alterations in pharmacokinetics**

The pharmacokinetic properties of an administered drug may be modified due to alterations in hemodynamics and/or in the so-called intrinsic clearance (the magnitude of drug transporting or metabolizing capacity of the liver in the absence of hemodynamic influences). The hepatic clearance is a product of blood flow and extraction and can be estimated by a simple mathematical equation. However, these estimations are not accurate, nor practical for use clinically since both hepatic perfusion and intrinsic clearance can be affected in advanced liver disease to unpredictable degrees. The situation is further complicated by shunting of blood around and within the liver, becoming a major determinant of drug disposition, in particular, first-pass extraction. Shunting is a major determinant of the disposition of high extraction compounds such as bile acids, which can be used as a measure of this parameter.

The impairment of drug metabolism is proportional to the liver dysfunction. Patients with well-compensated cirrhosis and near-normal synthetic function will have a lesser extent of impaired drug metabolism as compared with patients with decompensated cirrhosis with significant synthetic dysfunction and portal hypertension. Though various tests like liver function test, indocyanine green clearance, Child Pugh score, and Meld score are used for prediction of impaired liver function, no tests can yet determine drug dosing in these patients reliably. Drugs with first pass metabolism require reduction in oral dosages; for high clearance drugs both loading and maintenance dosages need adjustment whereas for low clearance drugs maintenance dose only needs adjustment. Whenever possible, measuring drug level in the blood and monitoring of adverse events should be done fairly frequently. No set guidelines have however, been developed for this purpose.

**Alterations in pharmacodynamics**

It is important to keep in mind the pharmacodynamic alterations in chronic liver disease in relation to certain commonly used drugs (Table 1). For example, sedative agents should be used with caution.
in patients with liver disease since they can precipitate hepatic encephalopathy. Both pharmacokinetic and pharmacodynamic alterations have been noted in patients with cirrhosis of the liver.

Response to diuretics and vasoconstrictors is blunted in cirrhosis. For any given level of furosemide, there is a decreased rate of sodium secretion in patients with cirrhotic ascites, irrespective of clinical responsiveness. Some of these disadvantages can be circumvented by using torsemide in place of furosemide, as the former also has altered pharmacokinetics leading to prolonged delivery of the active drug to the distal tubules. On the other hand, blunted response to vasoconstrictors may be due to a combination of several factors such as upregulation of NO synthase, alteration in ion channels of smooth muscles or alteration in receptor density. It is important to keep these in mind and monitor the drug dosage carefully to ward off any adverse effect.

**Table 1: Altered pharmacodynamics in patients with chronic liver disease**

<table>
<thead>
<tr>
<th>Altered response</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased susceptibility of patients to hepatotoxic reactions or other adverse effects</td>
<td>Acetaminophen, ACE inhibitors, aminoglycosides, β-lactam antibiotics, benzodiazepines and morphine, NSAIDs, pefloxacin</td>
</tr>
<tr>
<td>Blunted response to vasoconstrictors in portal hypertension</td>
<td>Furosemide, β-adrenergic agonists, angiotensin II, atrial natriuretic peptide, endothelin</td>
</tr>
</tbody>
</table>

*Taken from ref 3.

**Table 2: Antibiotics to be avoided in liver disease.***

<table>
<thead>
<tr>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol—higher risk of bone marrow suppression (markedly increased half life)</td>
</tr>
<tr>
<td>Erythromycin estolate—causes cholestasis</td>
</tr>
<tr>
<td>Tetracycline—dose related hepatotoxicity</td>
</tr>
<tr>
<td>Antituberculous therapy in combinations, pyrazinamide</td>
</tr>
<tr>
<td>Griseofulvin—contraindicated</td>
</tr>
<tr>
<td>Nalidixic acid</td>
</tr>
<tr>
<td>Nitrofurantoin, prolonged use</td>
</tr>
</tbody>
</table>

*Taken from ref 4.

more likely to occur in a patient who has also taken alcohol. Pharmacodynamic interactions between alcohol and other drugs are also common, particularly the additive sedative effects with benzodiazepines and also with some of the antihistamine drugs. Interactions may also occur with tricyclic antidepressants. The combination of NSAIDs and alcohol intake increases the risk of gastrointestinal haemorrhage.

**DRUG PRESCRIBING**

Gathering information from two recent reviews on the subject, I am giving below the rational use of some common drugs in patients with advanced liver disease.

1. **Antibiotics**

   Chronic liver disease patients are known to 5-7 fold increase in bacteremia because of suppressed immunity in them on account of several factors, the most predominant of them being defective bactericidal opsonic activity and neutrophil function. As a result they require frequently antibiotics for therapeutic or prophylactic purpose. It is therefore necessary to know which antibiotics are safe and if they need dosage alteration in patients with liver cirrhosis.

   Certain antibiotics should preferably be avoided (Table 2). They include macrolides like erythromycin, azithromycin, chloramphenicol, lincomycin, and clindamycin; they are excreted and detoxified by liver and hence the potential for their toxicity. Tetracyclines, isoniazid and Rifampin have prolonged half life in patients with liver cirrhosis. Metronidazole ketoconazole, miconazole, fluconazole, itraconazole, and nitrofurantoin pyrazinamide should be used with caution. Beta-lactam antibiotics can cause leucopenia, while amino glycosides can increase susceptibility to renal failure. Vancomycin can cause increased toxicity in patients with liver failure. Antibiotics which can produce hepatitis or cholestasis should be again used with caution. Certain antibiotics may even cause acute liver failure and hence their use should preferably be completely avoided (Table 3).

   Giving antituberculosis (ATT) drugs in chronic liver disease patients poses a special challenge. Indeed, cir-
rhotic patients with tuberculosis have significantly lower completion of Rifampicin + isoniazid ATT, higher hepatotoxicity, and higher mortality. In compensated liver disease (Child A), the usual 4 drug regime can be given and is well tolerated. However, in decompensated liver disease patients one or more hepatotoxic antituberculosis drug should be withheld.

Hepatotoxicity requires withdrawal, modification, and sequential reintroduction to achieve cure of tuberculosis. Using such hepatotoxic drugs in presence of cirrhosis or advance liver disease is a challenge. Recommended ATT in Child class A cirrhosis is the same as a non cirrhosis population but strict followup is required. In Child class B patients, pyrazinamide should be avoided and Isoniazid may not be given with rifampicin. Isoniazid or rifampicin with ethambutol and quinolones can be used for 12 to 18 months. In Child Class C patients, none of the hepatotoxic ATT drugs should be used and thus ethambutol, quinolones, and one second line agent may be used for 12 to 18 months.

Antifungal drugs like Ketoconazole and miconazole though hepatotoxic can be used in patients with cirrhosis but close monitoring of drug concentration in serum is recommended. Metronidazole dose is reduced by 50% in patients with severe cirrhosis and/or associated renal insufficiency. There is no information of safe use of nitrofurantoin, chloramphenicol, sodium fusidate and pyrazinamide but they are potentially toxic hence their use should be avoided in liver disease.4

2. Sedatives, Analgesics and Anesthetics

Endoscopic procedures are often necessary in patients with cirrhosis who may need sedation or short anesthesia. Benzodiazepines like midazolam have been traditionally used for this. Whilst a single dose of it is tolerated well by patients with compensated cirrhosis that may not be the case in those with decompensated cirrhosis. Fentanyl (opioid) elimination, on the other hand, is near normal in cirrhotics and can be used for sedation. Patients with opioid toxicity can be treated with naloxone. Propofol is however, preferred to benzodiazepines or opioids for endoscopic sedation for patients with decompensated cirrhosis due to its short half life and lower risk of inducing encephalopathy. The adverse effects of propofol are hypotension, tachycardia, hypoventilation, and prolongation of QT interval.

A. Anesthetic Agents

General Anesthesia can reduce the hepatic blood flow resulting into decompensation. Volatile agents and halothane should be avoided. The new agents like isoflurane, desflurane are not significantly metabolized by the liver and are therefore safe. Combination of agents like fentanyl may greatly reduce the need of anesthetic agents. Propofol is also a good agent for combination anesthesia.

B. Analgesics

Administering analgesics in patients with cirrhosis is tricky as they may precipitate severe complications like gastrointestinal bleeding, hepatic encephalopathy, hepatorenal syndrome, and mortality. Nonsteroid anti-inflammatory agents are contraindicated as they can cause GI bleeding and renal failure. Opioid analgesics should be used with caution as they may precipitate encephalopathy. Acetaminophen at a dose less than 2 gm/day is a reasonably safe option. In case of inadequate pain relief, tramadol 25 mg every 8 hours can be used. For intractable pain hydromorphone orally or fentanyl topical patch can be used. Combination of these drugs with tramadol should not be done. Neuropathic pain can be treated with nortriptyline, desipramine, and gabapentin, pregabalin with or without acetaminophen. Analgesic choice in patients with cirrhosis should be individualized depending on the etiology of cirrhosis, nutritional status, adherence, renal function, liver transplant candidacy, and drug-drug interaction.4,9

3. Anticonvulsants

Phenytoin, Carbamazepine, and valproate can be hepatotoxic. All the drugs can however, be used cautiously in patients with decompensated liver disease. The newer anticonvulsants like lamotrigine, topiramate also need lowering of the dosage in cirrhotic patients. Antidepressant, (selective serotonin reuptake inhibitors) like flu-

---

Table 3: Antibiotics causing hepatotoxicity*

<table>
<thead>
<tr>
<th>Hepatocellular injury</th>
<th>Cholestatic injury</th>
<th>Fulminant hepatic failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol, Clindamycin</td>
<td>Cephalosporins, Erythromycin</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Penicillin G, Amoxicillin</td>
<td>Penicillin G, Oxacillin, Cloxacillin</td>
<td>Trimethoprim-Sulfmethoxazole</td>
</tr>
<tr>
<td>Trimethoprim-Sulfmethoxazole</td>
<td>Floxacillin, Augmentin, Clarithromycin, Ketoconazole, PAS, Trovafoxacin</td>
<td></td>
</tr>
<tr>
<td>Amphotericin, Hydroxystilbamidine</td>
<td>Nitrofurantoin, Trimethoprim-Sulfmethoxazole</td>
<td></td>
</tr>
<tr>
<td>Ketoconazole, Itaconazole</td>
<td>5-fluorocytosine, griseofulvin</td>
<td></td>
</tr>
<tr>
<td>INH, Trovafoxacin, Oxacillin</td>
<td>Trovafoxacin, Thiabendazole</td>
<td></td>
</tr>
</tbody>
</table>

*taken from ref 4.
Prescribing in Patients with Liver Disease

Prescribing in Patients with Liver Disease

Voxamine, paroxetine, and fluoxetine need dose modification in patients with cirrhosis.9

4. Cardiovascular and Other Drugs

Patients with nonalcoholic steatosis-related cirrhosis have an increased incidence of dyslipidemia, hypertension, and coronary artery disease. Drugs like labetolol and methyldopa can cause severe hepatotoxicity and need frequent monitoring and should be used only when there are no other choices. Captopril, Amiodarone, and ticlopidine can cause hepatotoxicity and should be used with caution.

The details of dose adjustments on alpha blockers, ACE inhibitors, angiotensin II receptor antagonist, and other drugs used in cardiovascular diseases have been reviewed elsewhere in the recent past.10 Statins appear to be remarkably safe in patients with liver cirrhosis.11

Among antidiabetic drugs, biguanides (metformin), sulphonylureas (Chlorpropamide, glibenclamide, tolbutamide) and acarbose are avoided because of their toxicity. However, metformin can be used in patients with liver cirrhosis without renal insufficiency. Other antidiabetics like second-generation sulfonylurea like Glipizide, Glimepiride may be the drug of choice in patients with liver cirrhosis. Thiazolidinediones can cause drug hepatitis but can be used in reduced dosage with strict monitoring.9

Antiemetic metoclopramide and ondansetron require significant dose reduction in patients with cirrhosis. Proton pump inhibitors are preferable than H2 receptor antagonists but their dose should also be reduced to about half the usual dose.9

CONCLUSION

In conclusion, prescribing medicines in patients with liver disease is indeed challenging as almost 50% of the drugs in the physicians’ desk reference are known to cause liver injury. More than 100 drugs are incriminated in causing fulminant hepatic failure; only a few common ones have been mentioned in table 3 in this chapter. Furthermore, there are no clear tests which can identify altered drug metabolism in these patients. Thus, medications should be individualized depending upon the need, nutritional status, alternatives available and severity of liver disease. While giving a potentially hepatotoxic drug to a liver disease patient it is most important to monitor closely the clinical and biochemical parameters and to warn the patient and the family of the potential toxicity. Often clinicians have to choose between a devil and deep sea. Clinical judgement is paramount, but it should be backed by a sound knowledge of pharmacology and drug interactions.

ACKNOWLEDGEMENT

The author is grateful to Dr Deepak Amarapurkar (ref 4), Drs Anand and Chawla (ref 3) and National Medical Journal of India for giving me permission to reproduce tables and some sections of text from their articles.

REFERENCES